Drug-Eluting Stent Thrombosis
Results From a Pooled Analysis Including 10 Randomized Studies

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OBJECTIVES We compared the risk of stent thrombosis (ST) after drug-eluting stents (DES) versus bare-metal stents (BMS), and tested the hypothesis that the risk of DES thrombosis is related to stent length.

BACKGROUND Whether DES increase the risk of ST remains unclear. Given the very low restenosis rate after drug-eluting stenting, longer stents are frequently implanted for the same lesion length in comparison to BMS.

METHODS We included in a meta-analysis 10 randomized studies comparing DES and BMS. Overall, 5,030 patients were included (2,602 were allocated to DES and 2,428 to BMS). The risk of thrombosis after DES versus BMS was compared, and the relationship between the rate of DES thrombosis and stent length was evaluated.

RESULTS Incidence of ST was not increased in patients receiving DES (0.58% vs. 0.54% for BMS; odds ratio: 1.05; 95% confidence interval [CI]: 0.51 to 2.15; p = 1.000). The overall rate of ST did not differ significantly between patients receiving sirolimus- or paclitaxel-eluting stents (0.57% vs. 0.58%; p = 1.000). We found a significant relation between the rate of ST and the stented length (Y = 1.455 + 0.121 X; 95% CI for beta: 0.014 to 0.227; R = 0.716; p = 0.031). In patients with DES, mean stented length was longer in those suffering ST (23.4 ± 8.1 mm vs. 21.3 ± 4.1 mm, p = 0.025).

CONCLUSIONS Drug-eluting stents do not increase the risk of ST, at least under appropriate anti-platelet therapy. The risk of ST after DES implantation is related to stent length. (J Am Coll Cardiol 2005;45:954–9) © 2005 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have dramatically reduced restenosis in comparison with bare-metal stents (BMS) (1–11). Some initial reports warned of a possible increase in the risk of stent thrombosis (ST). However, whether ST is increased with the use of DES as compared with BMS has not been demonstrated, at least under appropriate antiplatelet therapy (1–11).

Given the very low restenosis rate after DES implantation, longer stents have frequently been implanted, assuming that optimizing immediate angiographic results as possible—even covering nonsignificant coronary lesions—is followed by better clinical outcomes. Some studies have shown that ST after BMS implantation is related to the stent length, rather than lesion length (12). We hypothesized that stented length may be related to the risk of ST and also to the use of DES. To test this hypothesis, we performed a meta-analysis of 10 studies that randomly compared DES and BMS. We also used these studies to compare the risk of ST after DES versus BMS implantation.

PATIENTS AND METHODS

Studies included in the analysis. We included 10 randomized studies comparing DES and BMS published before June 2004: Randomized study with sirolimus-coated Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (RAVEL) (1); SIRolImUS-Eluting balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (SIRIUS) (2); European multicenter randomized double-blind study of the SIRolImUS-Eluting balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (E-SIRIUS) (3); Canadian multicenter randomized double-blind study of the SIRolImUS-Eluting balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (E-SIRIUS) (3); Canadian multicenter randomized double-blind study of the SIRolImUS-Eluting balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (C-SIRIUS) (4); Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) (5); European evaluation of paclTaxel-Eluting Stent (ELUTES) (6); Treatment of de novo coronary disease using a single pAclitaXel eUting Stent (TAXUS)-I, -II, and -IV (7–9); and RX ACHIEVE Drug-Eluting coronary stent system In the treatment of patients with de noVo nativE coronaRy lesions (DELIVER) (10).

In the RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS trials, patients were randomly assigned either to slow-release sirolimus-DES (140 μg/cm²) or BMS (BX Velocity stent, Cordis Corp., Miami Lakes, Florida). In the ASPECT,
ELUTES, and DELIVER trials, a non-polymeric paclitaxel-DES was used (5,6,10). In the ASPECT trial, 176 patients were randomized in a 1:1:1 fashion to either paclitaxel 1.3 μg/mm², paclitaxel 3.1 μg/mm², or BMS (Supra-G stent, Cook Inc., West Lafayette, Indiana). In that study, 37 patients received cilostazol instead of thienopyridines in association with aspirin. This subgroup was excluded because this regimen is not the currently accepted antiplatelet course after coronary stenting. Other patients who did not receive any anti-platelet therapy were also excluded (5). In the ELUTES trial, patients were assigned to paclitaxel 0.2, 0.7, 1.4, and 2.7 μg/mm², or BMS (V-Flex Plus coronary stents, Cook Inc.) (6). In the DELIVER study, the ACHIEVE paclitaxel-DES (3.0 μg/mm²) and the Multilink-Penta BMS (Guidant Corp.) were compared (10). A polymeric paclitaxel-DES was evaluated in the TAXUS trials (7–9). In TAXUS-I, a slow-release paclitaxel-DES (1.0 μg/mm²) was compared with BMS (NIR, Boston Scientific Corp., Natick, Massachusetts) (7). In the TAXUS-II study, a first cohort of patients compared a slow-release paclitaxel-DES with BMS, and a second cohort evaluated a moderate-release paclitaxel-DES (8). Finally, in TAXUS-IV, the slow-release paclitaxel-DES was compared with BMS (Express, Boston Scientific Corp.) (9). Overall, 5,030 patients were included: 2,602 allocated to DES, and 2,428 to BMS.

Stenting procedure and antiplatelet therapy. In most studies, conventional stent implantation was mandated, although direct stenting was allowed in some trials (3,4). Conversely, most studies allowed post-dilation. In the studies in which the implantation of >1 stent was allowed, stents were overlapped in 28% to 36% of cases (2–4,9). In some studies, intravascular ultrasound was used to guide coronary stenting (5,7,8). In most of them, however, only some patients underwent intracoronary ultrasound either by inclusion in a sub-study or at the operator’s discretion. Aspirin was given to all patients indefinitely. Additionally, clopidogrel was given for one (5), two (1–4), three (6,10), or six (7–9) months. The duration of clopidogrel therapy tended to be longer after paclitaxel than sirolimus (4.2 ± 2.1 months vs. 2.0 ± 0.0 months, respectively, p = 0.056). Glycoprotein IIb/IIIa inhibitors were used at the operator’s discretion in most studies (1–4,6,8,9), although in some of them it was either not used or discouraged (5,7).

Statistical analysis. The review was conducted according to the Quality of Reports of Meta-Analyses of Randomized Clinical Trials (QUOROM) recommendations (13). The Reviewer Manager 4.1 (2000 Cochrane Collaboration) and the SPSS 10.0 (Chicago, Illinois) statistical packages were used.

Quantitative variables are expressed as mean ± standard deviation, and discrete variables as percentages. Associations between categorical variables were studied by the chi-square test or the Fisher exact test (in case any expected value is <5). Comparisons between two mean values were evaluated with the Student t or the Mann-Whitney tests, as appropriate (normally distributed and not normally distributed variables, respectively). The odds ratio (OR) for ST and late stent thrombosis (LST), and their 95% confidence interval (CI) were calculated comparing DES with BMS rates using raw data for each study and for the pooled population (intention-to-treat basis). The ST was classified as early and late (within or after more than one month after stenting). The fixed-effect model or the Der Simonian and Laird random-effect model (when p < 0.05 for Q test for heterogeneity) were used. The combined effect for the heterogeneity was calculated by taking the inverse variance estimated. The effect of each study was weighted for its number of patients.

To evaluate associations between two continuous variables, the curve fit regression analysis was used, weighting for the number of patients from each study. The estimated beta-coefficient as well as its 95% CI was also calculated. We contacted the principal investigator of all trials in which ≥1 DES ST occurred in order to compare DES ST with patients not suffering DES ST. Associations were considered statistically significant when p < 0.05.

RESULTS

Characteristics of the studies included for analysis. Table 1 provides the number of patients included in each study. Prevalence of diabetes ranged from 14% to 31%. The use of glycoprotein IIb/IIIa inhibitors ranged from 0% to 64%. Data from quantitative coronary analysis for each study are shown in Table 2.

Risk of ST with DES versus BMS. The rate of ST did not differ between DES and BMS (0.58% vs. 0.54%, respectively; OR: 1.05; 95%CI: 0.51 to 2.15; p = 1.000) (Fig. 1A). The rate of LST was also similar (0.25% vs. 0.25%, respectively; OR: 0.99; 95%CI: 0.35 to 2.84; p = 1.000) (Fig. 1B). After excluding non-polymeric paclitaxel studies (ASPECT, ELUTES, and DELIVER), the risk of both ST (0.65% vs. 0.55%; OR: 1.19; 95%CI: 0.51 to 2.77; p = 0.831) and LST (0.27% vs. 0.27%, respectively, for DES and BMS; OR: 0.99; 95%CI: 0.29 to 3.43; p = 1.000) was not different.

The rate of DES ST ranged from 0% to 2% among studies (Table 2), and it did not differ between patients receiving sirolimus and paclitaxel (0.57% [5 of 878] vs. 0.58% [10 of 1,724], respectively; p = 1.000). Of the 15 DES ST cases, 9 (60%) occurred within 30 days, whereas 6 (40%) were LST. The rate of LST did not differ signifi-
cantly between sirolimus- and paclitaxel-DES (0.11% [1 of 878] vs. 0.29% [5 of 1,724]; p = 0.670). Of the five late paclitaxel-DES ST, two occurred in the TAXUS-II, two in the TAXUS-IV, and one in the DELIVER trial. The only late sirolimus-eluting ST occurred in the SIRIUS trial. When comparing sirolimus-DES with polymeric paclitaxel-DES, no significant differences were found in the rate of ST (0.57% [5 of 878] vs. 0.73% [7 of 959], respectively; p = 0.776) and LST (0.11% [1 of 878] vs. 0.42% [4 of 959], respectively; p = 0.377). Non-polymeric and polymeric paclitaxel-DES showed no significant differences in the rate of ST (0.39% [3 of 765] vs. 0.73% [7 of 959], p = 0.527) and LST (0.13% [1 of 765] vs. 0.42% [4 of 959], p = 0.390).

### Relationship between stent length and risk of DES ST.

Using the curve fit regression analysis, the best fit was obtained with linear regression. We found a significant association between the incidence of ST and stented length that remained after weighting by the number of patients included in each study (Y = −1.455 + 0.121 X; 95% CI for coefficient beta: 0.014 to 0.227; R² = 0.121). The mean number of stents placed in patients with DES ST was 1.33 ± 0.62 (vs. 1.11 ± 0.32 in those without ST; p = 0.190) (difference 0.22; 95% CI: −0.12 to 0.56). A strong correlation was found between stent length and the number of stents placed (R = 0.875, p = 0.001).

No significant association was found between the rate of DES ST and other variables studied (Table 3).

### DISCUSSION

#### DES thrombosis.

The overall rate of ST after DES implantation was −0.6%, and did not differ between sirolimus and paclitaxel DES. This incidence is comparable to that of BMS (14). Owing to the possibility of delayed endothelialization and enhanced platelet aggregation after DES implantation, initial reports warned about the possibility of higher risk of ST (15,16). However, recent studies have reported a low incidence of DES thrombosis under prolonged therapy with aspirin plus thienopyridines, comparable to that of BMS, even in unstable clinical settings (17). No differences were found between sirolimus and paclitaxel-DES.
DES. However, the duration of thienopyridines treatment tended to be longer with paclitaxel; thus, a higher thrombogenicity of paclitaxel that might have been mitigated by a longer duration of dual anti-platelet treatment cannot be ruled out.

All study patients were under thienopyridines. The most striking factor associated with DES thrombosis is absence of treatment with ticlopidine/clopidogrel. In the ASPECT trial, the rate of DES thrombosis in patients receiving cilostazol instead of thienopyridines was 14.8% (4 of 27) (5). In another study, 30% of patients withdrawing ticlopidine early after DES implantation suffered ST (18). Of the 15 DES thrombosis cases, 6 (40%) were LST. This could be related to a delayed stent endothelialization (14), late stent malapposition (8), aneurysm formation, and even a localized hypersensitivity to the polymer (19). In comparison with BMS, late stent malapposition occurs more frequently after sirolimus-DES (9% in the SIRIUS trial and 21% in the RAVAL trial). However, in the TAXUS-II trial, late stent malapposition was not more frequent with paclitaxel-DES.

Figure 1. (A) Comparison between the rate of stent thrombosis in patients allocated to drug-eluting stents (DES) or bare-metal stents (BMS) in the randomized studies and in the pooled population. (B) Comparison between the rate of late stent thrombosis in patients allocated to DES or BMS in the randomized studies and in the pooled population. CI = confidence interval; OR = odds ratio.

![Figure 1](image1.png)

![Figure 2](image2.png)

Figure 2. Relation between stent length and the rate of drug-eluting stent (DES) thrombosis in the different studies included in the meta-analysis. CI = confidence interval.
than with BMS (8). Thus, these data should encourage us to prescribe prolonged combined antiplatelet therapy of aspirin plus thienopyridines, perhaps for at least one year. In the TAXUS-II trial, 2 of the 3 STs occurred between 6 and 12 months after DES implantation (8).

**Relationship between stent length and risk of ST.** The risk of DES thrombosis ranged from 0% to 2% among the trials. This incidence was significantly related to stent length. This also occurs with BMS, and has important implications, given the potential serious clinical consequences of ST (12). Probably, as stent length increases, it is more difficult to ensure that the stent is fully deployed and in contact with the vessel wall. In the TAXUS-II trial, lesion length was a predictor of late stent malapposition (20). In a very recent study, the total stent length was significantly associated with the risk of intra-procedural ST (24,25). Finally, intravascular ultrasound was not performed in cases suffering DES thrombosis. Therefore, the underlying mechanisms contributing to the physiopathology of DES thrombosis were not provided. At our center, we have performed a prospective study using intracoronary ultrasound in a series of patients suffering ST after BMS implantation. Stent under-expansion (75%), incomplete apposition (33%), and edge-dissection (17%) were frequently found (26). We can hypothesize that these mechanisms are also involved in DES thrombosis.

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